## SUMMARY OF SAFETY AND EFFECTIVENESS DATA

## I. GENERAL INFORMATION

| | |
|---|---|
| Device Generic Name: | tisilfocon A rigid gas permeable contact lens |
| Device Trade Name: | Menicon Z™ (tisilfocon A) rigid gas permeable (RGP) contact lens |
| Applicant's Name and Address: | Menicon Co., Ltd.<br>21-19 AOI, 3-CHOME, NAKA-KU<br>NAGOYA, AICHI 460-0006<br>JAPAN |
| Date(s) of Panel Recommendation: | None |
| Premarket Approval (PMA) Application Number: | P990018/S2 |
| Date of Notice of Approval to Applicant: | July 12, 2002 |

## II. INDICATIONS FOR USE

Menicon Z™ (tisilfocon A) spherical, aspheric, prism ballast toric and prism ballast multifocal lenses are indicated for daily wear for the correction of refractive error (myopia, hyperopia, presbyopia and/or astigmatism) in aphakic and non-aphakic persons with non-diseased eyes.

Menicon Z™ (tisilfocon A) spherical, aspheric, non-prism ballast toric and non-prism ballast multifocal lenses are indicated for extended wear (from 1 to 30 days between removals for cleaning and disinfection of the lenses, as recommended by the eyecare professional) for the correction of refractive error (myopia, hyperopia, presbyopia and/or astigmatism) in non-aphakic persons with non-diseased eyes.

The lens may be prescribed in spherical and aspheric powers ranging from -25.00 D to +25.00 D for daily wear and -25.00 D to +8.00 D for up to 30 days extended wear. Toric lenses are designed to correct up to 5.00 D of astigmatism and multifocal lenses to provide up to +3.00 D of reading add power for up to 30 days extended wear.

The lens may be disinfected using a chemical disinfection system only.

(The Menicon Z™ (tisilfocon A) rigid gas permeable contact lens was cleared for daily wear under K962006, K970019 and K972443.)

## III. CONTRAINDICATIONS

Menicon Z™ (tisilfocon A) contact lens should not be uses when any of the following conditions exist:

- Acute and subacute inflammation or infection of the anterior segment of the eye
- Any eye disease, injury, or abnormality that affects the cornea, conjunctiva, or eyelids
- Severe insufficiency of lacrimal secretion (dry eyes)

- Corneal hypoesthesia (reduced corneal sensitivity)
- Any systemic disease that may affect the eye or be exaggerated by wearing contact lenses
- Allergic reactions of ocular surfaces or surrounding tissues that may be induced or exaggerated by wearing contact lenses or use of contact lens solutions
- Allergy to any ingredient, such as mercury or Thimerosal, in a solution which is to be used to care for the Menicon Z™ (tisilfocon A) Contact Lens
- Any active corneal infection (bacterial, fungal, or viral)
- If eyes become red or irritated
- Incomplete healing following eye surgery

## IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the device labeling (attached).

## V. DEVICE DESCRIPTION

The Menicon Z™ (tisilfocon A) Rigid Gas Permeable Contact Lens is available as a daily wear spherical, aspheric, prism ballast toric or prism ballast multifocal design and as an extended wear lens for up to 30 days/29 nights in spherical, aspheric, non-prism ballast toric and non-prism ballast multifocal designs.

The lens material (tisilfocon A) is a thermoset copolymer derived from fluoro-methacrylate and siloxanylstyrene, bound by crosslinking agents. The lens is available in a light blue tint. The blue lens is tinted with color additive D & C Green No. 6. Also, a UV absorber (Benzotriazol) is added as an additive during the manufacturing process.

## VI. ALTERNATIVE PRACTICES AND PROCEDURES

The alternative practices and procedures to correcting vision by wearing the Menicon Z™ rigid gas permeable lenses include wearing other daily and extended wear rigid gas permeable contact lenses, soft contact lenses for daily and extended wear, spectacles, and corrective surgeries such as radial keratotomy, photorefractive keratectomy and LASIK.

## VII. MARKETING HISTORY

### A. United States

The Menicon Z™ (tisilfocon A) rigid gas permeable contact lens has been marketed in the United States for daily wear since October of 1996. The lens was approved for 7 day extended wear under PMA P990018 on July 11, 2000.

### B. International

The Menicon Z™ (tisilfocon A) rigid gas permeable contact lens is approved in Japan for daily and 7 day extended wear and in France and Germany for daily and extended wear up to 30 days.

## VIII. POTENTIAL ADVERSE EFFECTS OF DEVICE ON HEALTH

Potential adverse effects on health associated with extended wear contact lenses include eye problems such as corneal ulcers, epithelial microcysts, infiltrates and endothelial polymegathism. The risk of corneal ulcer has been shown to be greater among users of extended wear contact lenses than among users of daily wear contact lenses. The risk of extended wear users increases with the number of consecutive days that the lenses are worn between removals, beginning with the first overnight use. In addition, smoking increases the risk of corneal ulcers for contact lens users, especially when lenses are worn overnight or while sleeping. Strict compliance with the proper lens care regimen and wearing schedule is essential in minimizing risk.

## IX. SUMMARY OF PRECLINICAL STUDIES

The device is unchanged from that approved in the original PMA, P990018.

## X. SUMMARY OF CLINICAL STUDIES

### Primary Safety and Efficacy Study

#### Objective

The objective of this study was to examine the safety and efficacy of the Menicon Z™ high Dk rigid gas permeable (RGP) lens material for continuous (extended) wear of up to 30 days/29 nights when compared to a soft (hydrophilic) contact (SCL) lens approved for continuous wear of up to 7 days/6 nights.

### A. Study Design

The study was designed as a prospective, multi-center, concurrent cohort, controlled, open label clinical trial lasting 12 months after the initiation of extended wear (EW). A total of 661 subjects were enrolled at 24 investigational sites throughout the United States. Subjects were not randomized by lens modality due to the differences between RGP and SCL lenses; however, subjects were adapted daily wear (DW) users in the selected lens modality, with no prior EW experience. Subjects were assigned into either the Test lens (317 subjects/634 eyes) or the Control lens (a 58% water Group IV ionic lens) (313 subjects/625 eyes). Lenses were worn bilaterally for the duration of the study. Subject and investigator bias were minimized by distributing the study population, so that no one site contributed more than 6.4% of the study population to study analysis.

The Test lenses were worn for a minimum 2-week DW adaptation period, followed by a 30 day/29 night wearing schedule. Test subjects were required to wear their lenses for up to 30 days and then remove the lenses for one night prior to beginning a new cycle of extended wear. The lenses were cleaned and disinfected during this overnight removal. The Test lenses are durable lenses and were only replaced for cause.

The Control cohort was comprised of adapted DW soft (hydrophilic) contact lens wearers who were advanced to up to 7 days of “continuous” wear after enrollment, after a

minimum 2 week daily wear adaptation period with the Control lens. The Control lenses were worn based upon the labeled indications for up to 7 days extended wear. The Control lenses were scheduled for replacement on a weekly basis.

Eligibility Criteria

a) Inclusion Criteria

1. At least 18 years of age.
2. Refractive error between –20 and +12, with or without astigmatism (≤5.00 d) with acuity correctable to ≥ 20/25 in each eye.
3. Must be a successful daily wear soft or RGP contact lens wearer with no extended wear experience.
4. In good general health.
5. Willing and able to follow all instructions and keep appointments.
6. Must understand and sign the Informed Consent.

b) Exclusion Criteria

1. Presence of ocular or systemic allergies or disease which required removal of contact lenses more than twice a day.
2. Use of medications that had previously required discontinuation or limitation of contact lens wear.
3. Refractive correction that does not fall within the available parameters.
4. Functionally monocular subjects.
5. History of corneal trauma or ocular surgery (except cataract surgery with implant).
6. Clinically significant slit-lamp findings.
7. Ocular infection or history of corneal hypoesthesia.
8. Aphakia, keratoconus, or irregular cornea.
9. Inability to insert, remove, and handle contact lenses.
10. Pregnancy or lactation.
11. Infectious or immunosuppresive disease.
12. Diabetes.
13. Participation in any other clinical study within the past 30 days.

Lens Care Systems

The Test subjects were allowed to use the Claris® Care System or the Optimum System by LoBob® and were required to use Allergan ProFree/GP Weekly Enzymatic Cleaner on a monthly basis.

The Control subjects could use one of the following care systems, ReNu® Multi-Purpose Solution, Opti-Free® Express® Multi-Purpose Disinfecting Solution, AOSept® Disinfectant, or the QUICK CARE™ System. The protocol allowed for any soft contact lens approved rewetting solution to be used by the Control subjects.

Lens Wearing Directions and Evaluations

No standards exist for a break in wearing time, without it being counted as a break in extended wear. For this study, an appropriate extended or continuous wear time was defined as an extended wear period, without a break in wear time of greater than or equal to 6 hours.

All subjects underwent standardized ophthalmic examinations at enrollment and at the specified follow-up examinations. The subjects were also examined at unscheduled visits during the study period.

The examinations included the review and recording of subjective symptoms and objective findings along with visual acuity (VA), keratometry measurements, over-refraction and manifest refraction. The lenses were examined for defects, damage and cleanliness and the results of these examinations were recorded.

**1. Safety and Effectiveness Endpoints**

The primary safety endpoint analysis was focused on a comparison of the proportion of eyes with "threshold significant adverse events", which included the proportion of eyes with significant VA changes and slit lamp findings of corneal infiltrates, corneal staining, corneal edema, palpebral conjunctival findings and corneal neovascularization $\geq$ grade 3. For the primary safety endpoints**,** the Type I error (two-sided) is 5% and the Type II error is 20%.

Additional safety evaluations included the comparison of:

- Percentage of discontinuations and reasons for discontinuation
- Frequency and severity of reported adverse events
- Frequency and severity of subjective symptoms, problems or complaints
- Frequency and severity of positive slit lamp findings
- Proportion of eyes with changes in keratometry measurements greater than 1.0 diopter in any meridian
- Proportion of eyes with changes in refraction measurements greater than 1.0 diopter
- Proportion of eyes for which the final lens visual acuity differs from the initial best corrected visual acuity by two Snellen lines or greater

The evaluation of efficacy was based upon:

- The proportion of subjects in each cohort achieving and maintaining the targeted extended wear schedule
- An assessment of subject reported visual function for all subjects completing at least 6 months related to refractive error as reported using the Refractive Status and Vision Profile (RSVP) questionnaire.

Subjects were eligible for study participation if they were at least 18 years of age, had signed an Informed Consent form, and complied with the protocol-specified inclusion and exclusion criteria.

**2. Subject Assessments**

Subject examinations were scheduled to provide a two week daily wear period to allow the subjects to adapt to the lenses assigned for the study. At the 2-Week daily wear visit, the investigator either allowed the subject to start extended wear following the schedule appropriate for the assigned cohort, or discontinued the subject.

Extended wear follow-up visits were planned for 1 week, and 1, 3, 9, and 12 months after starting extended wear. The investigator also had the option of examining subjects at a 24-72 hour visit after the initiation of extended wear. Any other visits for any reason were recorded as unscheduled visits.

Adverse events were defined in the protocol as any hazardous, sight threatening condition such as: corneal ulcers, severe corneal abrasions >2mm in diameter, iritis, other ocular infections or inflammations, corneal scarring or permanent loss of vision. In addition, any adverse experience could be reported as an adverse event. Adverse events were additionally categorized as Serious Adverse Events, Significant Adverse Events, and Non-significant Adverse Events according to their severity.

Reasons for subject discontinuations included: subject or investigator decision; protocol deviations, lost to follow-up, comfort, positive slit lamp findings or adverse events, or unacceptable acuity. A completed subject is defined as completing the 12 month extended wear period of the study.

**3. Demographic Data**

The Test and Control cohorts were comparable with regard to gender, presence or absence of allergies, use of concurrent medications, and proportion of smokers. The two cohorts were significantly different in mean age, with the Test cohort older by an average of six years. In the Test cohort, the mean age was 40.9 years, with a range of 18 to 70 years. In the Control cohort, the mean age was 34.5 years, with a range of 18 to 65 years. This difference was expected due to the difference in rigid gas permeable and soft lens material modalities.

Refractive error ranged from +8.00 to –19.00 diopters for the Test cohort, with a mean of –4.42 diopters. Refractive error ranged from +7.00 to –10.25 diopters for the Control cohort, with a mean of –3.35 diopters. All subjects entered into the study were successful adapted daily wear wearers of the lens material modality used in the study.

## B. Data Analysis and Results

The statistical comparison is performed to evaluate safety and efficacy using the protocol-established variables outlined below:

### 1. Primary Safety Outcomes

There are two types of safety criteria, visual acuity (VA) changes and slit lamp findings. The VA criteria are a reduction in best corrected visual acuity (BCVA) in either eye of two or more Snellen lines from the dispensing BCVA, or a decrease in BCVA to below 20/40, whichever BCVA is less. Both scheduled and unscheduled visits were included in the analysis of whether a subject met the VA criteria. Safety determinations are based upon a comparison between the Test and Control cohorts.

### a. Best Corrected Visual Acuity Changes:

Only one Test completed subject met the reduction in BCVA criteria in the right eye only. The vision was reduced from 20/15 at the EW 3 month visit to 20/50 at the EW 6 month visit, but at two later scheduled visits, the VA was 20/20 and then 20/15.

### b. Slit Lamp Observations

The analysis of the safety criteria is also based on the following five slit lamp observations, corresponding with the original analysis variables that were not seen at the dispensing visit, but were seen in either eye at any scheduled or unscheduled visit.

1. Infiltrates of grade 3 or 4: (infiltrates of sufficient concern to warrant temporary or permanent discontinuation from lens wear).
2. Corneal Staining of grade 3 or 4
3. Stromal edema of grade 3 or 4: (Signs or symptoms of edema persisting beyond 2 hours from awakening &/or causing disrupted vision or with other signs.)
4. Palpebral Conjunctiva of grade 3 or 4: (Papillary response or hyperemia sufficient to warrant temporary or permanent discontinuation of wear.)
5. Corneal neovascularization of grade 3 or 4: (Vessel penetration >1.5 mm in a single quadrant, or >1 mm in multiple quadrants.)

Table 1 gives the number of subjects who met the above criteria at any of the visits. There were a total of 16 (5.1% of subjects initially enrolled) subjects in the Control group, and 20 (6.3%) in the Test group that met these criteria in either eye on any visit (scheduled or unscheduled). These percentages were not statistically significantly different from each other ($p=0.50$). The probability of such an event was unrelated to the subject's age. While subjects in the Test group were older than those in the Control group, there was no difference in age between those with and without these slit lamp defects.

TABLE 1
Threshold Significant Slit Lamp Events

| Visit | Control | Test |
|---|---|---|
| 2 wk DW | 1 | 1 |
| 24-72 hr EW | 1 | 2 |
| 1 wk EW | 2 | 3 |
| 1 month | 1 | 2 |
| 3 months | 2 | 4 |
| 6 months | 3 | 2 |
| 9 months | 3 | 3 |
| 12 months | 1 | 0 |
| Unscheduled | 8 | 11 |

| | Control | | Test | | |
|---|---|---|---|---|---|
| Total defects (OU counted as 1) | 22 | (10.8#) | 28 | (11.8#) | p=0.75** |
| Total follow-up visits | 2039 | | 2372 | | |
| Defect at scheduled follow-up visits | 14 | (7.4*) | 17 | (8.3*) | p=0.78** |
| Total scheduled follow-up visits | 1888 | | 2050 | | |
| Subjects with defects | 16 | (5.1%) | 20 | (6.3%) | $\chi^2 = 0.44$, p=0.50 |
| Subjects dispensed lenses | 313 | | 315 | | |

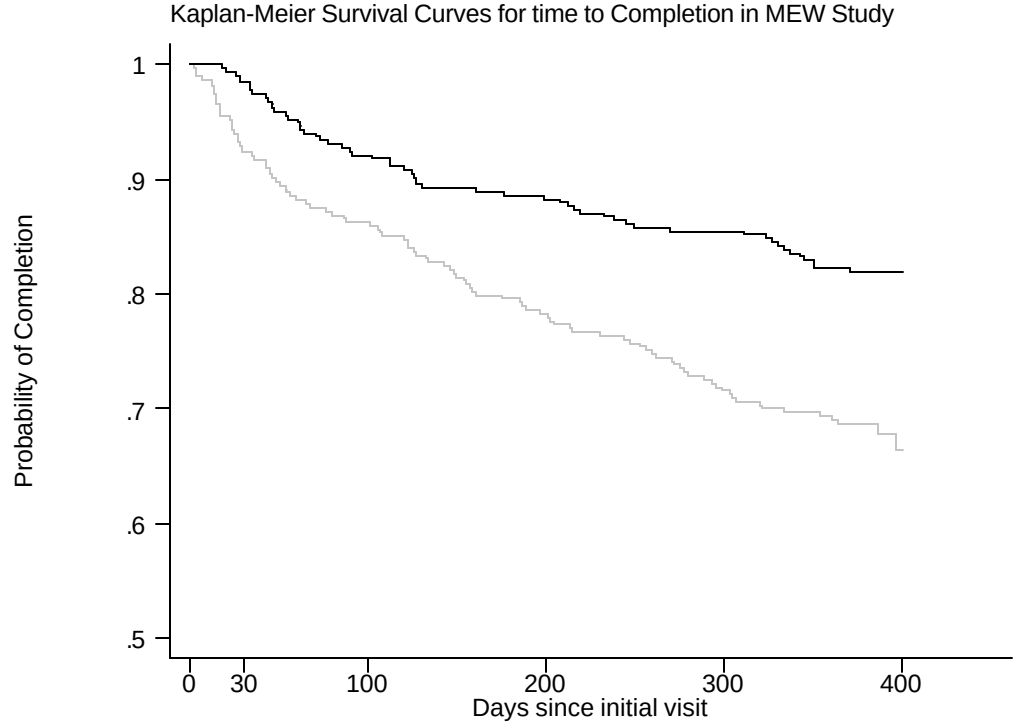
# defects in either eye per 1,000 visits
* defects in either eye per 1,000 scheduled visits
** Using Generalized Estimating Equations

There were 2039 total visits in the Control group and 2372 total visits in the Test group. This resulted in an event rate (event in either eye) of 10.8 per 1,000 subject visits (22/2039) in the Control group versus 11.8 per 1,000 subject visits (28/2372) in the Test group. This difference was not statistically significant (p=0.75). For scheduled visits alone, the rate is 7.4 per 1,000 scheduled visits in the Control group and 8.3 per 1,000 scheduled visits in the Test group (p=0.78).

To examine whether the contact lens wearing time was related to the likelihood of developing a slit lamp defect, average wearing time, in days, reported on the scheduled visit prior to which the slit lamp defect occurred was used. For those without any such defects, the wearing time reported at the 3 month extended wear visit was used. This was done because subjects had established their wearing patterns by this time. The average wearing time among Controls was 6.5 and 6.0 days for those without and with a slit lamp defect, respectively. Among the Test group, the mean wearing time was 21.0 days in those without a slit lamp defect, and 16.5 days among those who developed a defect. The interaction between wearing time and development of a slit lamp defect was not statistically significant (p=0.19).

There were no statistically significant differences in overall slit lamp findings by group. Figure 1 shows that there was no significant difference in time to first slit lamp defect by treatment group (Log rank p value=0.71).

FIGURE 1




Log Rank Test $\chi^2 = 18.33$ $p < 0.0001$

Relative Hazard = 0.50 (95%CI: 0.36, 0.69)

Top line is Test
Bottom line is Control

There were no statistical differences in the rates of the type specific findings by treatment group calculated as percent of subjects with any event type, except for 8 (2.5%) subjects with 3&9 o'clock corneal staining in the Treatment group compared with none in the Control group (p=0.007). The rate of binocular events was similar in the Test (1.3%) and the Control group (2.2%) (p=0.35).

### c. Adverse events

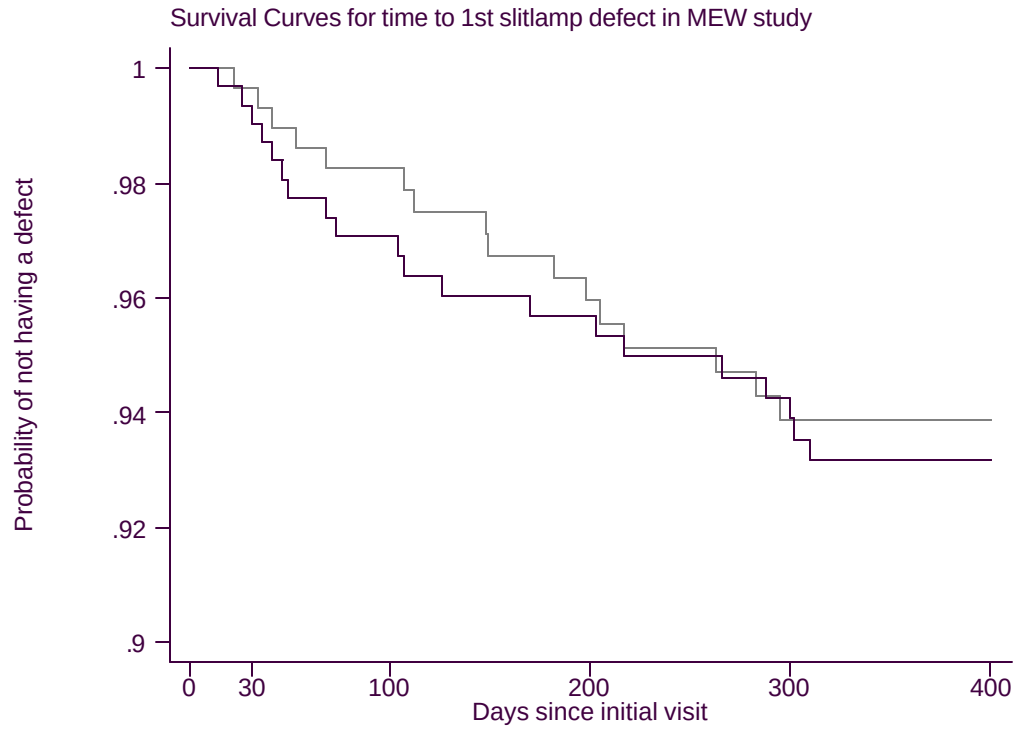
Adverse Events reported by the investigators are shown in Table 2. The columns headed "Subjects" present the number of subjects with a specific AE as a proportion of the total subjects in each cohort.

**TABLE 2**
**Adverse Events by Type**
**All Test and Control Subjects**

| CORNEAL ADVERSE EVENTS | Subjects | |
|---|---|---|
| **Inflammatory/Infectious Events** | **Test** | **Control** |
| Infiltrative Keratitis | 0.3% | 2.6% |
| Vascularized Limbal Keratitis | 0.6% | 0.0% |
| Corneal Ulcers | 0.3% | 0.3% |
| **Abrasions** | | |
| Foreign Body | 2.8% | 0.3% |
| Metabolic | 0.0% | 0.3% |
| Unknown | 0.0% | 0.6% |
| Chemical | 0.3% | 0.3% |
| **Edema** | | |
| Microcystic | 0.0% | 0.3% |
| **CONJUNCTIVAL ADVERSE EVENTS** | | |
| Bacterial | 0.6% | 2.9% |
| Viral | 0.3% | 0.0% |
| Allergic | 1.3% | 0.6% |
| GPC | 0.3% | 0.6% |
| Unknown | 0.3% | 0.6% |
| **MISCELLANEOUS ADVERSE EVENTS** | | |
| Sinus Infection | 0.0% | 0.3% |
| Trauma | 0.0% | 0.3% |
| Lens Displacement | 0.0% | 0.3% |
| Neurological | 0.0% | 0.3% |
| Episcleritis | 0.3% | 0.3% |
| Lacrimal Occlusion | 0.3% | 0.0% |
| Lens Awareness | 0.3% | 0.0% |
| **Total Subjects** | **317** | **313** |

Figure 2 shows the time to the first adverse event for each subject in the study. There were a total of 63 events (36 in Controls and 27 in the Test group) in 59 subjects (33 in Controls and 26 in the Test group). Of the 59 subjects with these adverse events, one subject in the Control group has 3 separate events, one subject in the Control group had two separate events, and one subject in the Test group had two separate events. The differences in rates of these events were not different between treatment and Control groups.

FIGURE 2




Log Rank Test: $\chi^2 = 0.14$ p =0.71

Relative Hazard = 1.13 (95%CI: 0.59, 2.19)

Top line is Control
Bottom line is Test

The events were classified into serious, significant and not significant. There were no "serious" events in either group. There was not a statistically significantly different rate of "significant events" among the Test group compared with the Control groups (8.2% versus 10.5%, respectively, p=0.31). There was also no significant difference in the time to the first significant adverse event. (Log rank p-value=0.15).

Events were classified by the clinicians as "definitely not related to the device", "unlikely related", "possibly related", "probably related", and "definitely related". There was a statistically significantly lower rate of adverse events considered "definitely related to the device" in the Test group compared with the Control group (none versus 2.2% respectively, Fisher's Exact two-sided p-value=0.007).

## 2. Efficacy Outcomes

### a. Lens Wearing Time

Table 3 contains the means, standard deviations, medians and maximum of the reported average days wearing of contact lenses at each scheduled visit. As per protocol, there are significant differences in wearing time between the Control and Test groups at all visits (even at the one week extended wear visit). At the 1week extended wear visit, the median wearing time is 7 days for both groups, but by 1 month, the Test group has a median wearing time of 21 days, which increases to 28 days at 3 months and 29 to 30 days thereafter, while the Control group remains at 7 days.

TABLE 3
Subject reports of average days of contact lens wear at scheduled visits

| | EW 1-Wk | EW 1-Mo | EW 3-Mo | EW 6-Mo | EW 9-Mo | EW 12-Mo |
|---|---|---|---|---|---|---|
| Controls | | | | | | |
| Mean (SD) | 5.9 (1.8) | 6.4 (1.5) | 6.5 (3.7) | 6.5 (1.1) | 6.7 (1.9) | 6.5 (1.0) |
| Median (Max) | 7.0 (10) | 7.0 (14) | 7.0 (60) | 7.0 (14) | 7.0 (30) | 7.0 (7) |
| Test | | | | | | |
| Mean (SD) | 6.3 (2.0) | 18.6 (10.9) | 20.9 (11.7) | 23.9 (13.3) | 24.0 (9.2) | 23.8 (9.4) |
| Median (Max) | 7.0 (13) | 21.0 (35) | 28.0 (90) | 29.0 (171) | 29.0 (30) | 30.0 (30.) |

All mean wearing times for Control and Test groups are statistically significantly different.

Table 4 gives the proportion wearing the lenses as per schedule (for example, at 12 months, 95.2% of Controls are wearing the lenses on average between 6 and 8 days, and 67.8% of the Test group are wearing the lenses an average of 28-30 days). In general, the compliance with lens wear as recommended is quite good, although there is some fraction of those in the Test group who are wearing lenses on a weekly schedule, rather than monthly (12.8% at the 12 month follow-up are between 6-8 days on average).

TABLE 4
Distribution of average days of wear at scheduled visits

| | EW 1-Wk | EW 1-Mo | EW 3-Mo | EW 6-Mo | EW 9-Mo | EW 12-Mo |
|---|---|---|---|---|---|---|
| Control | | | | | | |
| < 6 | 63 (22.3) | 31 (11.5) | 30 (11.8) | 15 (6.3) | 12 (5.5) | 10 (4.8) |
| 6-8 | 215 (76.0) | 236 (87.7) | 222 (87.4) | 220 (92.8) | 205 (93.6) | 200 (95.2) |
| 9-27 | 5 (1.8) | 2 (0.7) | 1 (0.4) | 2 (0.8) | 1 (0.5) | 0 |
| 28-30 | 0 | 0 | 0 | 0 | 1 (0.5) | 0 |
| 30+ | 0 | 0 | 1 (0.4) | 0 | 0 | 0 |
| Total | 283 | 269 | 254 | 237 | 219 | 210 |
| Test | | | | | | |
| < 6 | 59 (20.3) | 37 (13.0) | 23 (8.2) | 12 (4.6) | 13 (5.1) | 10 (3.9) |
| 6-8 | 215 (74.1) | 53 (18.6) | 54 (19.4) | 36 (13.6) | 25 (9.8) | 34 (13.2) |
| 9-27 | 16 (5.5) | 75 (26.3) | 60 (21.5) | 51 (19.3) | 44 (17.2) | 40 (15.5) |
| 28-30 | 0 | 114 (40.0) | 135 (48.4) | 162 (61.4) | 174 (68.0) | 174 (67.4) |
| 30+ | 0 | 6 (2.1) | 7 (2.5) | 3 (1.1) | 0 | 0 |
| Total | 290 | 285 | 279 | 264 | 256 | 258 |

The distribution of the visit reported wearing times over all extended wear visits after 1 month is presented in Table 5 below.

Table 5
Average Lens Wearing Time
Reported after the 1 Month Visit
Completed Subjects

| Wearing Time (in Days) | Test | Control |
|---|---|---|
| 0-7 | 18.0% | 99.4% |
| 8-14 | 8.3% | 0.4% |
| 15-21 | 7.2% | 0.0% |
| ≥22 | 66.5% | 0.2% |

A total of 82.0% of the completed Test subjects reported extended wearing times at scheduled visits after 1 month that exceeded 7 days of wear. Of these, the majority of the completed Test subjects (66.5%) reported wearing times of greater than 21 days.

The distribution of the days of wear from subject diaries is presented in Table 6 below:

Table 6
Extended Wearing Time
By Subject Diary
Completed Eyes

| Wearing Time (Consecutive Days) | Test | Control |
|---|---|---|
| 0 to 7 Days | 11.7% | 73.1% |
| 8 to 14 Days | 9.8% | 11.7% |
| 15 to 21 Days | 8.3% | 2.2% |
| ≥22 Days | 70.2% | 13.0% |

The results indicate that the proportion of the total wearing days of 22 days or greater is 70.2% for the completed Test eyes. This result compares well with the visit reported average wearing times where 66.5% of the average wear reported was for periods of 22 consecutive days or greater.

**b. Quality of Life Evaluation (RSVP)**

The comparison of baseline to final responses on the Refractive Status and Vision Profile (RSVP) questionnaire was the second of the efficacy measures discussed in the protocol. The RSVP was designed to provide an evaluation of subject satisfaction with their vision and vision correction. The results of this evaluation indicated modest improvements in vision-related function and symptoms. Both Test and Control Cohorts reported some improvement satisfaction in going from daily to extended wear.

**4. Additional Safety Endpoints**

**a. Discontinuations**

Over the duration of the study, 59 of the 317 Test cohort subjects (18.6%) and 103 of the Control cohort subjects (32.9%) were discontinued from the study. The Control cohort subjects had a higher discontinuation rate due to Protocol Violations and Lost to Follow-up.

Three (3) Test and 9 Control cohort subjects were discontinued for Positive Slit Lamp Findings. The 3 Test cohort subjects were discontinued for limbal desiccation (1 subject), increased neovascularization and 3&9 staining (1 subject), and raised epithelial hypertrophy at the sites of old 3&9 scars (1 subject). The 9 Control cohort subjects were discontinued for neovascularization (2 subjects), GPC (2 subjects), mild microcysts and trace edema (1 subject), mild microcysts and mild staining (1 subject), mild infiltrates, non-staining and asymptomatic (1 subject), trace palpebral conjunctival findings (1 subject), and mild infiltrative keratitis (1 subject).

Three (3) Test and 7 Control cohort subjects were discontinued for Adverse Events. The 3 Test subjects were discontinued for an epithelial corneal defect (1 subject), solution sensitivity (1 subject), and marginal ulcerative keratitis (1 subject). The 7 Control cohort subjects discontinued for Adverse Event were discontinued for: severe epithelial microcysts (1 subject), keratitis from contact lens overwear (1 subject), bacterial conjunctivitis (1 subject), sector field defect (1 subject), peripheral corneal ulcer (1 subject), focal infiltrative keratitis (1 subject), and marginal infiltrative keratitis (1 subject).

TABLE 7
Reasons for Discontinuation By Cohort

| | Test Subjects | | Control Subjects | |
|---|---|---|---|---|
| Subjects Enrolled | 317 | | 313 | |
| Lost to Follow-up | 12 | 3.8% | 29 | 9.3% |
| Protocol Violation | 9 | 2.8% | 21 | 6.7% |
| Comfort | 12 | 3.8% | 16 | 5.1% |
| Subject Decision | 13 | 4.1% | 11 | 3.5% |
| Positive Slit Lamp Findings: | | | | |
| Related to Study Lens | 3 | 0.9% | 8 | 2.6% |
| Unrelated to Study Lens | 0 | 0% | 1 | 0.3% |
| Adverse Event | 3 | 0.9% | 7 | 2.2% |
| Investigator Decision | 4 | 1.3% | 4 | 1.3% |
| Unacceptable Visual Acuity | 0 | 0% | 1 | 0.3% |
| Study Product Not Dispensed | 0 | 0% | 0 | 0% |
| Other: | 3 | 0.9% | 5 | 1.6% |
| Total Subjects Discontinued | 59 | 18.6% | 103 | 32.9% |

**b. Slit Lamp Findings**

Table 8 presents the percentage and average severity of positive findings by category throughout the extended wear phase of the study for all eyes.

Table 8
Incidence and Average Severity of Positive Slit Lamp Findings
Completed and Discontinued Eyes Pooled

| Finding | Test Cohort EW Total | | Control Cohort EW Total | |
|---|---|---|---|---|
| Sample Size | 3901 | | 3405 | |
| | Incidence | Average Severity | Incidence | Average Severity |
| Epithelial Edema | 1.1% | 1.3 | 3.6% | 1.1 |
| Epithelial Microcysts | 1.6% | 1.0 | 7.0% | 1.3 |
| Stromal Edema | 0.3% | 1.3 | 1.1% | 1.3 |
| Corneal Neovascularization | 7.4% | 1.1 | 14.5% | 1.1 |
| Corneal Staining | 12.4% | 1.2 | 17.4% | 1.2 |
| 3&9 Corneal Staining | 22.2% | 1.2 | 0.4% | 1.5 |
| Limbal & Bulbar Hyperemia | 13.2% | 1.2 | 15.4% | 1.2 |
| Palpebral Conjunctiva | 8.1% | 1.3 | 22.5% | 1.3 |
| Infiltrates | 0.2% | 2.1 | 0.8% | 1.7 |
| Other: | 6.4% | | 6.7% | |

For the extended wear phase of the study, for all visits and all eyes, 0.1% of the Test cohort and 0.2% of the Control cohort slit lamp findings were rated as Grade 3 or greater (moderate or severe). The distribution of moderate or severe positive slit lamp findings as a proportion of the eyes in each cohort is presented in Table 9.

Table 9
Distribution of Moderate & Severe Positive Slit Lamp Findings
Incidence By Cohort
All Completed and Discontinued Eyes Pooled

| | Grade 3-Moderate | | Grade 4-Severe | |
|---|---|---|---|---|
| | Test | Control | Test | Control |
| Sample Size | 634 | 625 | 634 | 625 |
| Epithelial Edema | 0.0% | 0.5% | 0.0% | 0.0% |
| Epithelial Microcysts | 0.0% | 1.4% | 0.0% | 0.3% |
| Corneal Staining | 1.6% | 0.3% | 0.0% | 0.6% |
| 3&9 O'clock Staining | 2.1% | 0.0% | 0.0% | 0.0% |
| Limbal & Bulbar Hyperemia | 1.9% | 1.0% | 0.0% | 1.4% |
| Palpebral Conjunctiva | 1.4% | 3.2% | 0.0% | 0.3% |
| Infiltrates | 0.6% | 0.3% | 0.0% | 0.0% |
| Slit Lamp Other | 0.9% | 0.3% | 0.0% | 0.5% |

**c. Symptoms, Problems and Complaints**

Except for Lens Needs Cleaning and "other", the symptoms, problems and complaints reported during the study were similar in incidence between the Test and Control cohorts during the extended wear phase of the study.

Lens needs cleaning was reported at 11.5% of all examinations for the Test cohort as compared to 4.9% for the Control cohort. This is expected since the Control lenses were discarded every 7 days while the Test lenses are durable lenses and were replaced during the study at a rate of 1 lens per subject per year.

Other symptoms were reported at 11.2% of all extended wear examinations for the Test cohort and at 15.1% of all extended wear visits for the Control cohort and were primarily Dryness.

**d. Keratometric and Refractive Changes**

A total of 104 (8.5%) Test cohort eyes and 55 (4.7%) Control cohort eyes had keratometry measurements change by more than 1.00 diopter. The maximum change was 3.50 diopters with the Test lens and 2.63 diopters with the Control lens. The reasons for the changes as reported by the investigators were: changes related to extended wear, differences between exam rooms or observers, normal corneal changes, or corneal molding/sphericalization of the cornea.

A total of 70 (5.7%) Test cohort eyes and 10 (0.9%) Control cohort eyes had a refractive error change greater than 1.00 diopter. The maximum change was 3.50 diopters with the Test lens and 2.63 diopters with the Control lens. The reasons for the changes as reported by the investigators were primarily lens induced corneal flattening, operator or instrument

error, and the creation or recovery from corneal edema. These findings indicate that neither the Control or the Test contact lens caused any adverse changes in corneal shape.

The reasons cited by the investigators for changes in refraction for the Test cohort were: changes due to continuous wear versus daily wear, normal changes, changes from going to higher Dk lenses, and corneal molding with RGP wear. For the Control cohort, the reasons cited included: normal changes, probable edema undetectable by slit lamp, and 1 subject had refractive surgery performed 1 month prior to exit (exited for protocol non-compliance).

**e. Visual Acuity**

Best corrected visual acuities recorded at the initial visit were compared to the lens visual acuities at the final visit for all Test and Control eyes and all VA decreases of 2 Snellen lines or greater were identified. For the Test cohort there were 16 changes (2.5%) of 2 lines or greater over the duration of the study and for the Control cohort there were 20 changes (3.2%) of 2 lines or greater over the course of the study.

Changes reported for the 16 Test eyes were explained by the investigators as resulting from:

- increased or progressive myopia (4 eyes);
- normal VA fluctuation (5 eyes);
- increase in cataract density (2 eyes from 1 subject);
- lens coating/deposits (2 eyes);
- due to dryness (1 eye);
- lens power checking as weak (1 eye);
- and unknown (1 eye).

Changes reported for the 20 Control eyes were explained by the investigators as resulting from:

- normal VA fluctuation (7 eyes);
- increase in cylinder (3 eyes);
- refraction change –0.25 sph/-0.50 cyl (2 eyes);
- increase in corneal astigmatism (1 eye);
- change in Rx (1 eye);
- due to dry eyes (1 eye);
- due to astigmatism (4 eyes);
- monovision near eye (1 eye).

The proportions and the reasons cited for the changes from the best corrected visual acuities to the lens visual acuities are similar between the Test and the Control cohort eyes.

The proportion of eyes achieving lens visual acuities of 20/20 and 20/30 were compared from the dispensing to the final exit visit for both the Test and the Control cohort eyes. These proportions are illustrated in Table 10 below:

Table 10
Proportion of Lens VA's

| Eyes with Lens VA 20/30 or better: | Dispensing | Final Visit |
|---|---|---|
| Completed Test Eyes | 99.2% | 99.6% |
| Completed Control Eyes | 100.0% | 100.0% |
| Discontinued Test Eyes | 96.5% | 95.3% |
| Discontinued Control Eyes | 99.0% | 99.4% |
| **Eyes with Lens VA 20/20 or better:** | **Dispensing** | **Final Visit** |
| Completed Test Eyes | 88.8% | 83.5% |
| Completed Control Eyes | 93.6% | 83.8% |
| Discontinued Test Eyes | 82.5% | 80.2% |
| Discontinued Control Eyes | 89.8% | 77.6% |

The proportion of eyes achieving lens visual acuities of 20/20 and 20/30 were similar between the Test and the Control eyes and support the efficacy of the study contact lenses.

**f. Lens Replacements**

Lens replacement rates are not comparable between the Test lenses and the Control lenses due to the difference in lens materials used. The Test lenses are a durable RGP lens, designed for continuous use over a long period of time and replacement only for cause. The Control lenses are planned replacement lenses that were replaced on a weekly basis. The difference between the replacement schedules means that replacements of the Control lenses could be subsumed in the planned replacement schedule, whereas the Test lens replacements would only be for a specific need.

Given this difference, the difference in the number of lenses replaced for cause between the Test and the Control cohorts is expected. The Test cohort replaced 348 lenses over the duration of the study (completed and discontinued eyes pooled). This results in a replacement rate of approximately 1 lens per subject per year.

The most frequently cited reasons for replacement for the Test cohort were Other (32.8% - mostly Loss), Parameter (Rx) Changes (29.0%) and Unacceptable VA (11.5%). The most frequent reasons cited for the 85 lenses replaced for the Control cohort were Parameter (Rx) Changes (55.3%) and Unacceptable VA (21.2%).

**Corneal and Endothelial Evaluation**

Two of the sites recruited for the clinical study performed a corneal and endothelial evaluation. Corneal thickness was measured to compare corneal swelling resulting from edema. Corneal thickness was measured at OSU with the Cornea-gage II (Sonogage, Cleveland, OH) ultrasonic pachometer and at CWRU with the CompuScan (Storz, St. Louis, MO) pachometer. Measurements were done on the right eye at the Dispensing visit, the 2 Week Daily Wear visit, and the 1 Week, 6 Month and 12 month Extended Wear visits. The average of six ultrasonic pachometry measurements was recorded at

each of these visits. Diurnal fluctuation in corneal thickness was controlled for by scheduling follow-up visits at the approximate same time of day as the baseline visit.

Both the Ohio State University and Case Western Reserve University sites used the Konan NonContact Robo specular microscope for endothelial evaluations. These microscopes were calibrated by the manufacturer and calibration was monitored before, during and after the study by the investigators. The subject was instructed to watch the fixation light in primary gaze and an image was captured from the central corneal endothelium of both eyes. After image capture, the data was stored and later, all contiguous cells with visible borders were dotted in the center by the same examiner. A minimum of 100 cells per eye was dotted for each subject. Endothelial cell analysis was automatically performed by the endothelial camera software and the cell density, coefficient of variation (CV) (standard deviation of cell area/mean cell area) and percentage of six-sidedness was recorded for each eye.

The study of the central corneal thickness evaluated whether there was a difference in corneal thickness change in subjects who wore the control soft contact lens for 7 day/6 night extended wear and subjects who wore the Test RGP lenses for 30 day/29 night extended wear in a controlled clinical trial. The results of the study demonstrated a significant ($p=0.03$) increase in corneal thickness in the Control lens cohort as compared to the Test lens cohort. This observation is due to the higher level of oxygen permeability with the Test RGP lenses.

The endothelial evaluation looked at the density and six-sidedness of the endothelial cells over the duration of the controlled study. The final conclusion of this evaluation was that the Test lens wearers in this study did not have significant endothelial cell morphology changes after one year of nearly continuous contact lens wear.

## XI. CONCLUSIONS DRAWN FROM THE STUDIES

The results of the preclinical and clinical studies provide reasonable assurance of the safety and efficacy of the Menicon Z™ RGP lens for the subject population, refractive conditions and specified duration of wear. The clinical endpoints measured in this study for the Menicon Z™ RGP lens for continuous (extended) wear of up to 30 days/29 nights are comparable to a soft (hydrophilic) contact lens for continuous wear of up to 7 days/6 nights. Although the potential exists for minor differences in physiological response by gender for the target population, minimal number of clinically significant differences are of clinical importance for this device. Therefore, FDA has concluded that the subject lenses are safe and effective when worn in accordance with the approved labeling.

## XII. PANEL RECOMMENDATION

In accordance with the provisions of section 515(c)(2) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Ophthalmic Devices Panel, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel. However, homework assignments were made individually to three panel members in order to confirm the conclusions from the internal FDA clinical review. The panel reviews did not raise any additional clinical issues that were unique to this device or

different from those identified in the internal review. All three panel members recommended approval of the device for extended wear up to 30 days.

## XIII. CDRH DECISION

FDA issued an approval order on _____

## XIV. APPROVAL SPECIFICATIONS

Directions for use: See the labeling

Hazards to Health from Use of the Device: See the Indications, Contraindications, Warnings, Precautions and Adverse Events in the labeling.

Postapproval Requirements and Restrictions: See approval order.